Large scale plant-based production: ISOs and cGMPs

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01 December 2021

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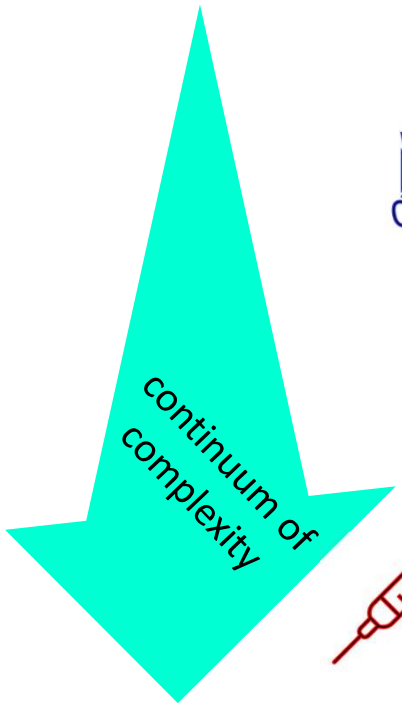
COMPLIANCE REQUIREMENTS:

Which industry?



Research reagents

Environmental / chemical testing

Food / Cosmetics

Medical Devices (diagnostics)

Pharmaceutical – active ingredient

Pharmaceutical – medicinal products

human / veterinary

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COMPLIANCE REQUIREMENTS:

What products?

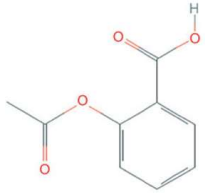
E.g. Pharmaceutical

Oral solid dosage

Injectable, sterile

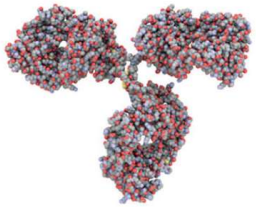
sub-continuum

Aspirin 180 Da



"Generics"

Monoclonal antibody
150 000 Da



Inherent variability
"Biosimilar"

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Wah, Hock, Kian. 2020
https://www.cphi-online.com/46/resourcefile/06/80/92/gea_containment_v2_Sept2016.pdf
https://www.prudentialuniforms.com/services/cleanroom/cleanroom-uniforms-and-apparel/nfpa-70e-fr/

REGULATION: Pharma, IVDs

How? *Gazetted Acts & Regulations*

Who? *Competent / Regulatory Authority (FDA, EMA, SAHPRA)*

SAHPRA South African Health Products Regulatory Authority

QUALITY

SAFETY

EFFICACY / PERFORMANCE

Quality Management System

Product technical file

AND / OR

Preclinical & Clinical

1 Site License: Manufacturer

Inspection / Certification

2 Product Registration

Technical File / Dossier Assessment

LEGISLATION (ACT 101)

REGULATIONS

GUIDANCES / STANDARDS

This is where the GMPs and ISOs fit in.

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Pharmaceutical Quality System

Quality Management (Prev. QA)

"all arrangements" re: quality

Good Manufacturing Practices

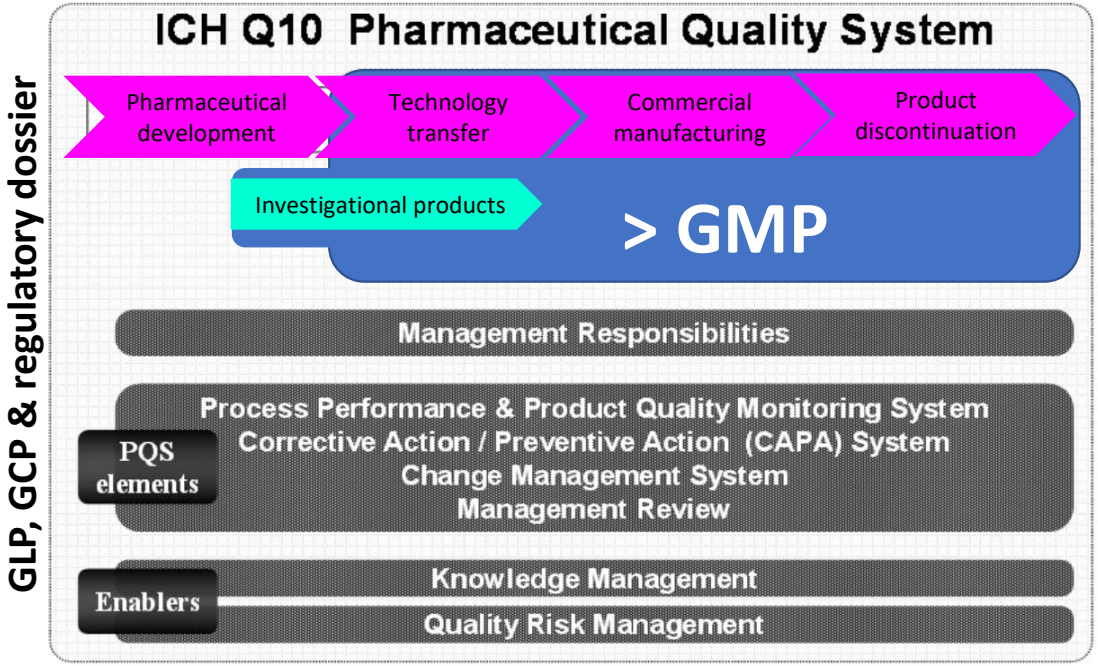
Consistency, risk*, specified quality

Quality Control

Sampling, testing, release

* contamination, cross-contamination, mix-up

PQS >



Broad alignment with ISO 9001 Quality Management Systems

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Pharmaceutical GMPs:

EU

PIC/S ↔ SAHPRA South African Health Products Regulatory Authority . . . ICH harmonisation for better health

1. PQS
2. Personnel
3. Infrastructure
4. Documentation
5. Production
6. QC
7. Outsourcing
8. Recall
9. Inspection

Part I - Basic Requirements for Medicinal Products (9 chapters)

Part II - Basic Requirements for Active Substances used as Starting Materials

Annexes (19) → ISO

Annex 1 Manufacture of Sterile Medicinal Products

Annex 2 Manufacture of Biological active substances and medicinal products for Human Use

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Pharmaceutical GMPs:

Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use (2018 update):

Type and source of material	Example product	Application of EU Annex 2 GMP for biologicals to manufacturing steps shown in blue for API and grey for API and medicinal product			
Biotechnology - fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting (GAP)	Initial extraction, isolation, purification, modification	Formulation, filling

Plants as a starting material

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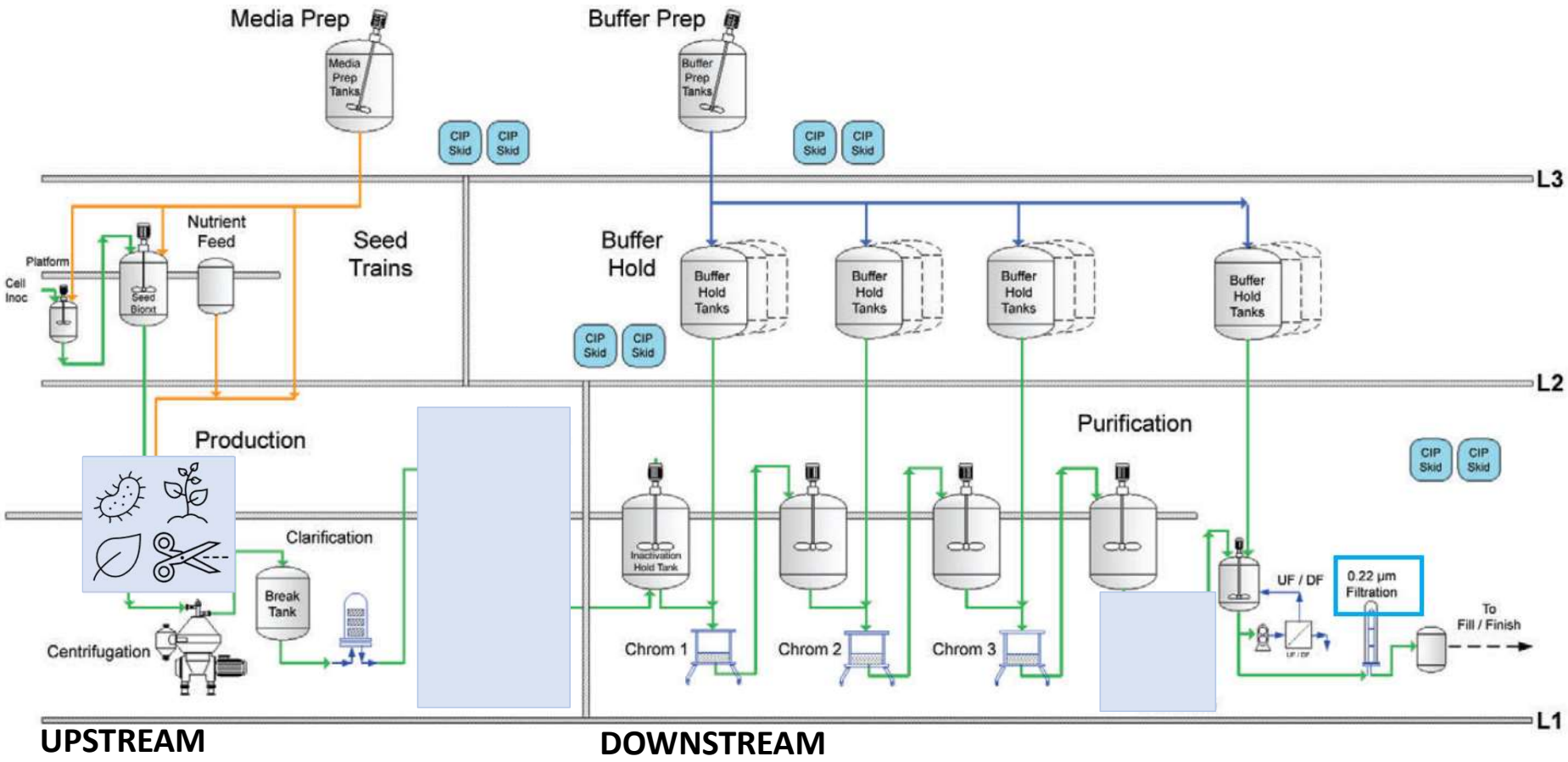

Adapted from ISPE, 2013. Baseline Guide Biopharmaceutical Manufacturing Facilities. Vol 2.

API Characterization emphasis.

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Biozeen media preparation vessel

Alfa Laval continuous centrifuge

Cytiva large-scale chromatography

Biozeen CIP station

Syntegon Purified Water and pure steam systems

Syntegon small batch isolator for filling

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Single-use disposable & closed systems

https://www.pall.com/en/biotech/single-use-solutions.html

https://www.biopharmadynamics.co.uk

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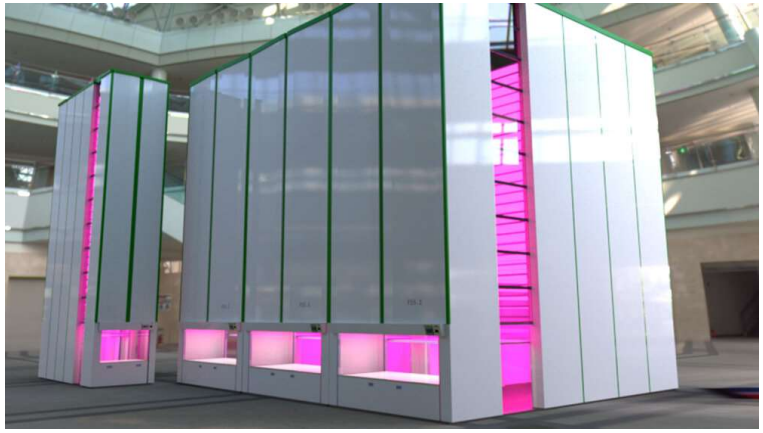
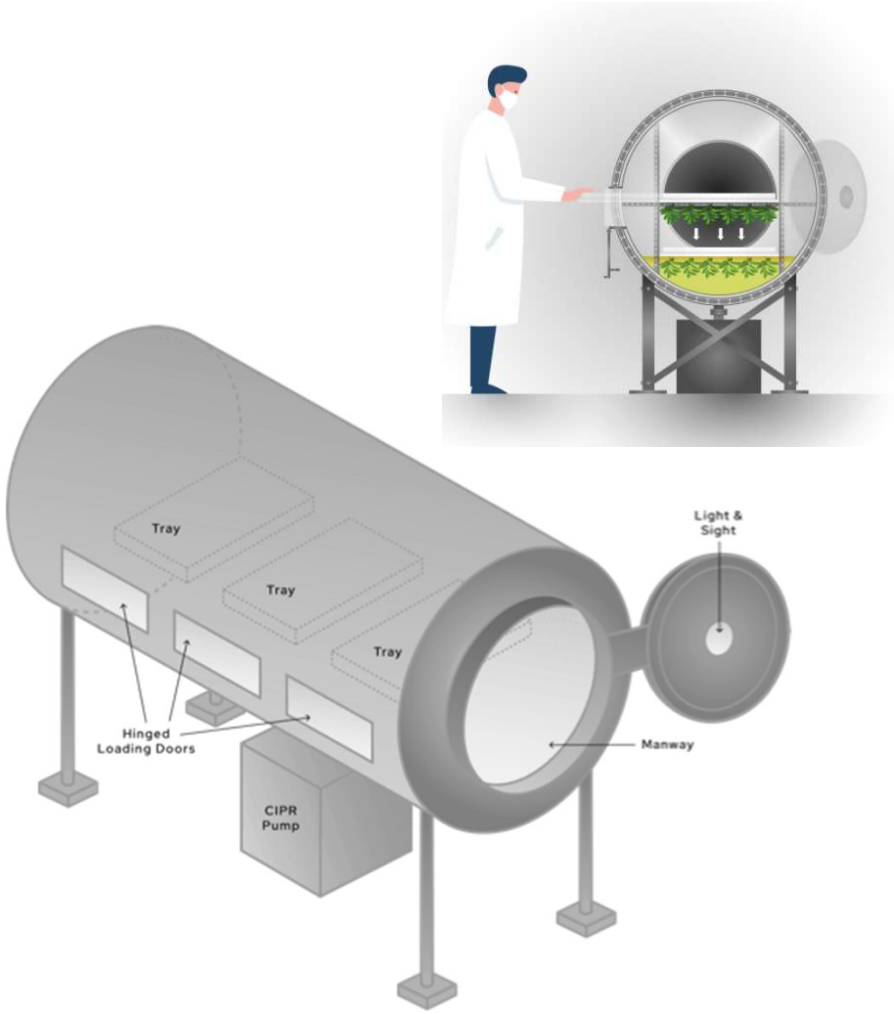
https://ifarm.fi/blog/2020/05/the-germination-chamber



https://www.inno-3b.com/



https://ibioinc.com/cdmo-services/factory-solutions/

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INTERNATIONAL STANDARD

ISO

Food safety management syste
Requirements for any organiza
the food chain

Cosmetics — Good Manufacturing Practices (GMP) — Guidelines on Good Manufacturing Practices

Cleanrooms and associated controlled environments —

Part 1:
Classification of air cleanliness by particle concentration

Packaging for terminally sterilized medical devices —

Part 2:
Validation requirements for forming, sealing and assembly processes

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ISO 22000

EU

CROSS-CONTAMINATION IN SHARED FACILITIES

Annex 8	Sampling of Starting and Packaging Materials
Annex 9	Manufacture of Liquids, Creams and Ointments
Annex 10	Manufacture of Pressurised Metered D
Annex 11	Computerised Systems (revis
Annex 12	Use of Ionising Radiation in the Manufa
Annex 13	Manufacture of Investigational Medicin Detailed Commission guideline of 8 De products pursuant to the second parag the date of entry into application of Reg
x	Manufacture of Products derived from
x 15	Qualification and validation (into op
nex	Certification by a Qualified Person and
nex	New - Parametric release (De Further information on the consultation
Annex 19	Reference and Retention Samples

ICH harmonisation for better health

- Q1A - Q1F Stability
- Q2 Analytical Validation
- Q3A - Q3E Impurities
- Q4A - Q4B Pharmacopoeias
- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- Q11 Development and Manufacture of Drug Substan
- Q12 Lifecycle Management
- Q13 Continuous Manufacturing of Drug Substances
- Q14 Analytical Procedure Development

FDA

Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Part II: Basic Requirements for Active Substances used as Starting Materials

PIC/S

AIDE-MEMOIRE

INSPECTION OF BIOTECHNOLOGY MANUFACTURES

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Reagent for MEDICAL DEVICES:

- **Suppliers** to test kit manufacturers are not directly regulated

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- **Medical device (incl. In-Vitro Diagnostic IVD) manufacturers** are regulated.
  - "Historically underregulated"
  - Changing fast!

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https://www.news24.com/citypress/news/in-depth-the-tangled-web-of-medical-device-regulation-in-sa-20200903

EU IVDR 2017/746

In Vitro Diagnostic Medical Devices Regulation, May 2022

Risk Class D, designated Notified Body performs conformity assessment of:

- Quality management system (similar to Site License)
- Technical documentation (GSPR)
- Product quality assurance (reference lab)

HIERARCHY PRESENTATION .....

CHAPTER 1 – REGIONAL ADMINISTRATIVE .....

CHAPTER 2 – SUBMISSION CONTEXT .....

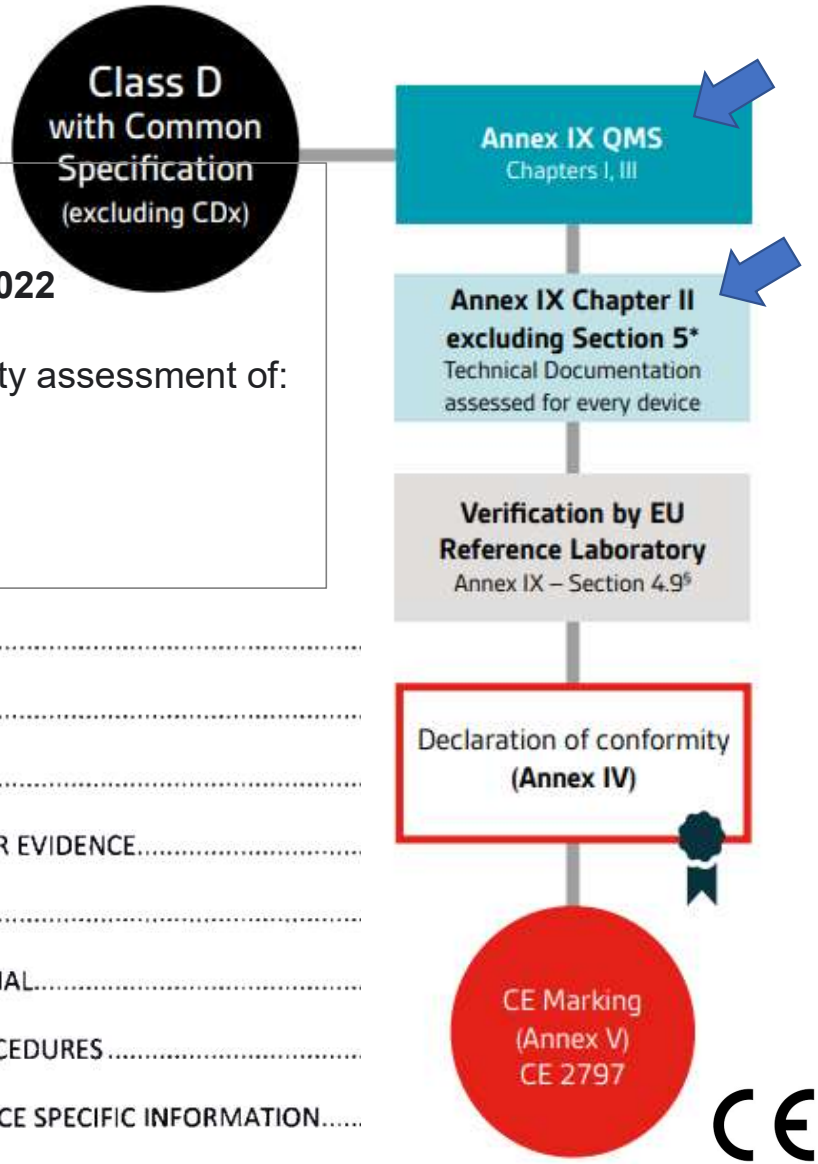
CHAPTER 3 – ANALYTICAL PERFORMANCE AND OTHER EVIDENCE.....

CHAPTER 4 – CLINICAL EVIDENCE .....

CHAPTER 5 – LABELLING AND PROMOTIONAL MATERIAL.....

CHAPTER 6A – QUALITY MANAGEMENT SYSTEM PROCEDURES .....

CHAPTER 6B – QUALITY MANAGEMENT SYSTEM DEVICE SPECIFIC INFORMATION.....



BSI credit

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International Organization for Standardization

The internationally accepted quality standard for medical device establishments is:

INTERNATIONAL STANDARD **ISO 13485**

Medical devices — Quality management systems — Requirements for regulatory purposes

- Based on ISO 9001
- Specific to the design and manufacture of MDs
- Applies to MD manufacturers **and their suppliers**

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SAHPRA
South African Health Products Regulatory Authority

SA Regulations relating to Medical Devices and IVDs Medical Gazette No. 40480

- Site License Import/Export/Manufacture/Wholesale/Distribute (requires certified QMS - 13485)
- Product registration - call-up schedule (not yet, transitional arrangements, some "quasi-reg" – evidence of safety, efficacy, quality)
- Covid exemptions (Wits test lab, temporary registration)

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https://www.news24.com/citypress/news/in-depth-the-tangled-web-of-medical-device-regulation-in-sa-20200903

Reagent for MEDICAL DEVICES:

- Suppliers to test kit manufacturers are not directly regulated

ISO 13485

ISO 14971

- Test kit medical device manufacturers are regulated.

QMS Supplier Management System
- Supplier Risk Ranking
- Quality Contracts
- Supplier QMS Audits
- Supplier Performance Monitoring

- Step 1: QMS / Site license

ISO 13485: QMS for Medical Devices

ISO 14971: Risk Management for MDs

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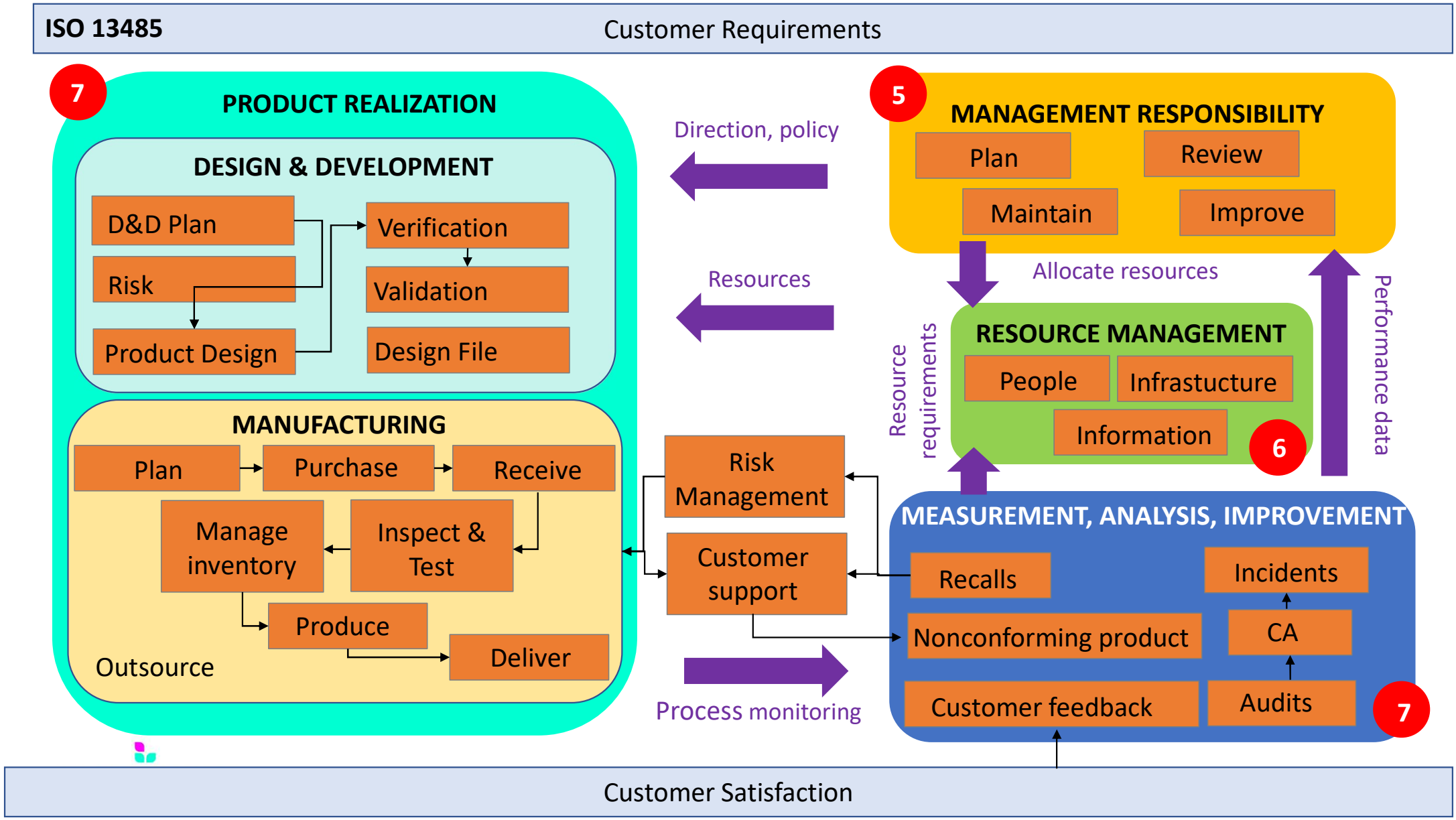
ISO 13485
Customer Requirements
7
PRODUCT REALIZATION
DESIGN & DEVELOPMENT
D&D Plan
Risk
Product Design
Verification
Validation
Design File
MANUFACTURING
Plan
Purchase
Receive
Manage inventory
Inspect & Test
Produce
Deliver
Outsource
Direction, policy
Resources
Risk Management
Customer support
Process monitoring
5
MANAGEMENT RESPONSIBILITY
Plan
Review
Maintain
Improve
Allocate resources
Resource requirements
RESOURCE MANAGEMENT
People
Infrastucture
Information
6
Performance data
MEASUREMENT, ANALYSIS, IMPROVEMENT
Recalls
Incidents
Nonconforming product
CA
Customer feedback
Audits
7
Customer Satisfaction

Challenge

- Market size
- Local skills & experience – industrial biologicals
- Funding opportunities?
- Regulatory processes
- Regulatory acceptance

Opportunity

- Regional collaboration
- Biovac, National Bioproducts, etc
- “Africa-aware”
- SAHPRA new model
- More regulatory harmonization / routes / collaboration

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